Eur J Clin Chem Clin Biochem
1995; 33:405–410

Dual Porphyria of Coexisting Variegata and Cutanea Tarda[1, 2])

By *Ina Sieg*[1], *Lalit K. Bhutani*[2] and *Manfred O. Doss*[1]

[1] *Abteilung für Klinische Biochemie im Fachbereich Humanmedizin der Philipps-Universität, Marburg/Lahn, Germany*
[2] *Department of Dermatology and Venereology, All-India Institute of Medical Sciences, Ansari Nagar, New Delhi, India*

(Received January 18/May 2, 1995)

Summary: While porphyria cutanea tarda and porphyria variegata are independent diseases, we report on seven rare cases with a coincidence of these two different porphyrias in one individuum.

The mutual clinical symptom was a cutaneous photosensitivity, which is a major symptom in porphyria cutanea tarda and a facultative one in porphyria variegata. Additionally, five patients had also experienced episodes of acute abdominal pain, which were in three cases accompanied by neurological symptoms, thus offering evidence for an acute hepatic porphyria, such as porphyria variegata.

Determination of urinary porphyrin metabolites revealed a porphyria cutanea tarda-like excretion pattern with an elevation of uroporphyrin (mean 1134 nmol/24 h, range 563–4052, normal ≤ 30) and heptacarboxyporphyrin (mean 389 nmol/24 h, range 64–830, normal ≤ 4). In all patients, however, urinary coproporphyrin was also increased, reaching levels too high for porphyria cutanea tarda but typical for porphyria variegata (mean 1788 nmol/24 h, range 142–4168, normal ≤ 120). Fecal porphyrin excretion also resembled the variegate-type with a high concentration especially of protoporphyrin (mean 628 nmol/g dry weight, range 401–1018, normal ≤ 151), accompanied by an increase of coproporphyrin (mean 194 nmol/g dry weight, range 75–409, normal ≤ 37). The urinary porphyrin precursors 5-aminolaevulinic acid and porphobilinogen were markedly elevated only in one patient, who was in an acute porphyric phase at the time of investigation. The activity of uroporphyrinogen decarboxylase in erythrocytes was considerably decreased in six of our cases (33–64%) and slightly diminished in the other one (83% of normal activity).

Those metabolic excretion profiles, supplemented by the cutanea tarda-associated uroporphyrinogen decarboxylase deficiency, reflect an intermediate pattern with characteristics of both porphyria cutanea tarda and variegata, as was confirmed by comparison with 15 cases of porphyria variegata and 10 cases of porphyria cutanea tarda.

Introduction

Porphyrias are mainly hereditary diseases, each one reflecting a partial genetic defect of one of the enzymes along the heme biosynthetic pathway (1, 2).

Porphyria cutanea tarda or chronic hepatic porphyria, resulting from uroporphyrinogen decarboxylase[3]) deficiency, is the most frequent porphyria (estimated incidence in Germany ~ 20–50 : 100 000) (2) and can also be toxically induced by polyhalogenated hydrocarbons like hexachlorobenzene (1). Porphyria variegata, an

[1]) Presented in part at the "International Meeting on Porphyrin Metabolism and Iron Metabolism", April 30–May 4, 1992, Papendal, The Netherlands, and at the symposion "Photobiology and Phototherapy", VII International Congress of Dermatology, New Delhi, India, February 26–March 2, 1994.

[2]) This study was supported by the Hans-Fischer-Gesellschaft, Munich.

Tab. 1 Clinical symptoms in dual porphyria of variegata and cutanea tarda.

Patient	Sex	Year of birth	Age [a] at diagnosis	Porphyria variegata				Chronic hepatic porphyria
				abdominal	cardiovascular	neurologic	cutaneous	liver affection
1	♀	1975	12	+	n.k.*	n.k.	+	n.k.
2	♀	1963	21	+	Ø	+	+	+
3	♀	1955	34	Ø	Ø	Ø	+	+
4	♀	1950	38	Ø	n.k.	n.k.	+	n.k.
5	♀	1948	31	+	+	+	+	+
6	♂	1954	30	+	Ø	Ø	+	Ø
7	♂	1951	32	+	Ø	+	+	Ø

* n.k. = not known

acute hepatic porphyria with protoporphyrinogen oxidase[3]) defect, has a lower incidence of approximately 1 : 100 000 in Germany (2).

Hereditary porphyrias are rare diseases by themselves; even more rare are forms of dual porphyria, i.e. the coexistence of two different gene defects in one individuum. We present here seven cases of a coinciding porphyria variegata and porphyria cutanea tarda.

Patients and Methods

The clinical data of our patients are compiled in table 1. Two of them came from India (1 and 2), the other five were Germans. Apart from two brothers (6 and 7) they were not related.

Urinary porphyrin precursors 5-aminolaevulinic acid and porphobilinogen were determined by ion-exchange chromatography and absorption spectrophotometry, urinary and fecal porphyrins by high performance thin-layer chromatography in combination with absorption spectrophotometry and spectrofluorometry (3). Coproporphyrin isomers were analysed by high performance liquid chromatography and absorption photometry (4). Uroporphyrinogen decarboxylase was measured in red cell lysates according to the method previously described (5).

Statistical evaluation was performed by *Wilcoxon*'s, *Mann*'s and *Whitney*'s U-test.

Results

Clinical evaluation

All patients (tab. 1) revealed a cutaneous photosensitivity of varying degrees, the most frequent symptom being an increased fragility of the skin with superficial bullae and erosions, which subsided leaving small scars (1–5), or with erythema (6, 7). Hypertrichosis and hyperpigmentation in the face were observed in patient 2, while patient 6 also complained about pruritus.

However, signs of acute porphyria, namely recurring episodes of abdominal pain often accompanied by nausea and vomiting, were the predominating symptoms in patients 1, 2, 5 and 7, thus directing diagnostic suspicion towards the manifestation of an acute hepatic porphyria. Neurological symptoms were epileptic seizures and unconsciousness (patient 2), hypesthesia (2 and 5), slight paresis (7) and psychic symptoms (depression in patient 5 and change of personality in patient 7).

In patients 3, 4 and 6, the cutaneous symptoms prevailed with abdominal symptoms being discrete (6) or absent (3 and 4). Therefore, these patients were admitted under the suspicion of chronic hepatic porphyria, i.e. porphyria cutanea tarda. Liver affection, a characteristic finding in porphyria cutanea tarda (6, 7), was found in patients 2 (increased urinary coproporphyrin I proportion, see below), 3 (increased aminotransferases) and 5 (increased urinary coproporphyrin I proportion, see below; liver biopsy: intrahepatic cholestasis, necrosis and fatty degeneration of single hepatocytes).

Family studies could not be performed apart from the investigation of a sister of the two brothers 6 and 7. The sister, born in 1943, suffered from porphyria cutanea tarda; histologically, a chronic hepatitis with moderate fibrosis was determined.

Pathobiochemical evaluation

Urinary and fecal porphyrin metabolites of the patients were investigated and compared to 10 cases of porphyria cutanea tarda and 15 cases of porphyria variegata (figs. 1–3 and tab.2). The metabolite excretion profiles of our seven patients revealed an intermediate pattern with characteristics of both porphyria variegata and cutanea tarda.

The increase of urinary coproporphyrin, in one case accompanied by a distinct elevation of the porphyrin precursors 5-aminolaevulinic acid and porphobilinogen, and the fecal porphyrin pattern with distinctly elevated

[3]) Enzymes:
5-Aminolaevulinate synthase (EC 2.3.1.37)
Protoporphyrinogen oxidase (EC 1.3.3.4)
Uroporphyrinogen decarboxylase (EC 4.1.1.37)

excretion rates especially of protoporphyrin and also of coproporphyrin, offer a constellation characteristic for porphyria variegata. However, the high values of urinary uroporphyrin and heptacarboxyporphyrin are typically seen in porphyria cutanea tarda (tab. 3), as is the reduction of erythrocyte uroporphyrinogen decarboxylase activity (tab. 4). In six of our patients uroporphyrinogen decarboxylase activity ranged between 33 and 66% of healthy controls, only one (patient 7) reached the near normal level (83%). Red blood cells contained normal amounts of protoporphyrin (data not shown).

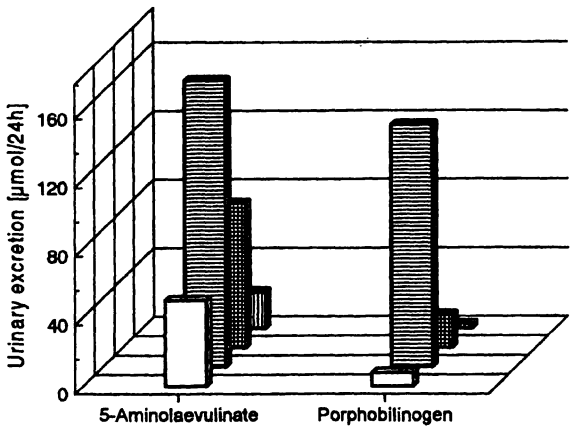

Fig. 1 Excretion of urinary porphyrin precursors: dual porphyria versus cutanea tarda and variegata.
□ normal range, ▤ porphyria variegata, ▦ dual porphyria, ▥ porphyria cutanea tarda

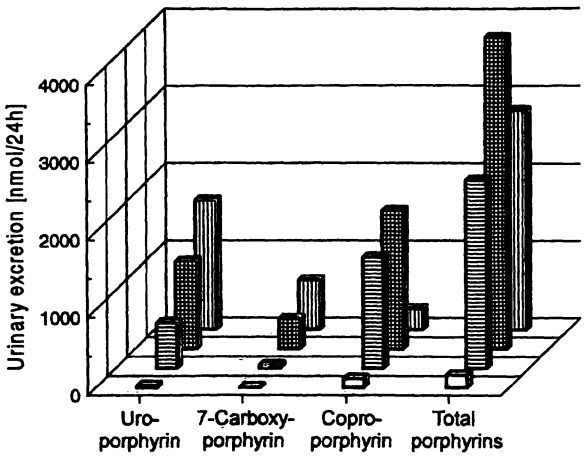

Fig. 2 Excretion of urinary porphyrins: dual porphyria versus cutanea tarda and variegata.
□ normal range, ▤ porphyria variegata, ▦ dual porphyria, ▥ porphyria cutanea tarda

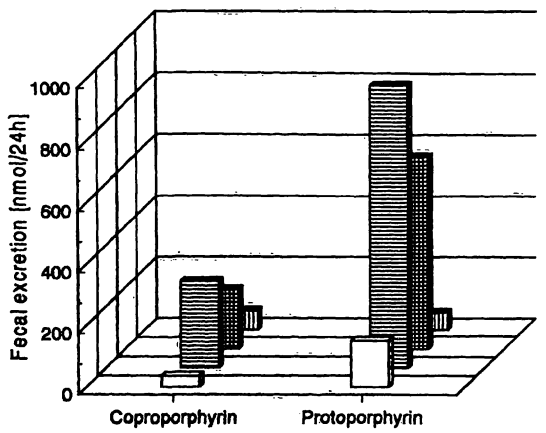

Fig. 3 Excretion of fecal porphyrins: dual porphyria versus cutanea tarda and variegata.
□ normal range, ▤ porphyria variegata, ▦ dual porphyria, ▥ porphyria cutanea tarda

Urinary coproporphyrin isomers I and III were determined in three cases; two of them (patient 2 and 5) showed an increased proportion of isomer I (50% and 55%, respectively, normal ≤ 31%), while in patient 7 isomer III dominated both in urine (84%, upper normal value 83%) and feces (78%, upper normal value 40%) in accordance with porphyria variegata (4, 8). Patient 2 also excreted an elevated fecal coproporphyrin III proportion of 57%.

Discussion

Dual porphyrias are rare and have so far been reported as combinations of acute intermittent porphyria and porphyria variegata (9), acute intermittent porphyria and porphyria cutanea tarda (10), as well as hereditary coproporphyria and congenital erythropoietic porphyria (11). We present seven cases of a coinciding porphyria variegata and porphyria cutanea tarda, as has first been described by *Day* and coworkers in the South African population (12). Variegate porphyria, also known as "South Africa genetic porphyria", has a comparatively high incidence in the white South African population of approximately 250 : 100 000 (13). Elsewhere, variegate occurs far less frequently (2). To our knowledge, only one single case report of a possible coexisting porphyria variegata and cutanea tarda has been published since in 1987 (14). We present the first case collection of this dual porphyria outside Africa.

The extraordinary urinary and fecal porphyrin patterns in our seven patients reveal characteristics both of porphyria cutanea tarda and variegata. Urinary coproporphyrin as well as fecal protoporphyrin and coproporphyrin excretion did not significantly differ from the pattern of 15 variegate cases (tab. 3); the same was found for urinary porphyrin precursors (5-aminolaevulinic acid and porphobilinogen), which were consistent with latent (n = 6) or overt (n = 1) variegata, thus offering a metabolite profile compatible with protoporphyrinogen oxidase deficiency (1, 15). With most excretion parameters indicating porphyria variegata, urinary uroporphyrin and heptacarboxyporphyrin levels were found to be exceptionally high for porphyria variegata, all the more for latent variegate, directing suspicion more towards porphyria cutanea tarda (1, 16). Indeed, statistical evaluation (tab. 3) gave no significant difference between our

Tab. 2 Excretion of urinary and fecal porphyrin metabolites: dual porphyria in comparison to cutanea tarda and variegata.

	Urine						Feces	
	5-Amino-laevulinate	Porpho-bilinogen	Uro-porphyrin	Hepta-carboxy-porphyrin	Copro-porphyrin	Total porphyrins	Copro-porphyrin	Proto-porphyrin
	[µmol/24 h]	[µmol/24 h]	[nmol/24 h]	[nmol/24 h]	[nmol/24 h]	[nmol/24 h]	[nmol/g]	[nmol/g]
Porphyria variegata (n = 15)	167* (13–487)**	141 (1.5–639)	586 (16–3408)	47 (3–188)	1437 (148–2930)	2433 (176–6009)	284 (28–714)	923 (123–2293)
Porphyria cutanea tarda (n = 10)	21 (11–33)	2.5 (1–4)	1669 (235–4043)	644 (166–1518)	273 (98–417)	2833 (586–6263)	62 (6–176)	57 (21–151)
Dual porphyria (n = 7)	84* (19–196)	19 (2–101)	1134 (563–4052)	389 (64–830)	1788 (142–4168)	4031 (1221–9972)	194 (75–409)	628 (401–1018)
Reference range	2–50	0.5–8	4–30	0–4	21–120	25–165	5–37	21–151

*mean ** range

Tab. 3 Statistical evaluation of excretion patterns by *Wilcoxon*'s, *Mann*'s and *Whitney*'s U-test: dual porphyria versus cutanea tarda and variegata.

	Urinary				Fecal	
	Σ (5-Amino-laevulinate, porphobilinogen)	Uro-porphyrin	7-Carboxy-porphyrin	Copro-porphyrin	Copro-porphyrin	Proto-porphyrin
Dual porphyria vs. porphyria cutanea tarda	s. ($p < 0.005$)	n. s. ($p > 0.05$)	n. s. ($p > 0.05$)	s. ($p < 0.001$)	s. ($p < 0.005$)	s. ($p < 0.001$)
Dual porphyria vs. porphyria variegata	n. s. ($p > 0.1$)	s. ($p < 0.01$)	s. ($p < 0.001$)	n. s. ($p > 0.2$)	n. s. ($p > 0.2$)	n. s. ($p > 0.1$)

s. = significantly different ($p < 0.05$); n. s. = not significantly different ($p > 0.05$).

patients and a porphyria cutanea tarda control group regarding uro- and heptacarboxyporphyrin.

To exclude the possibility that the high uro- and heptacarboxyporphyrin levels were indirectly caused by the protoporphyrinogen oxidase defect, we investigated erythrocyte uroporphyrinogen decarboxylase activity, which was markedly reduced in six and moderately diminished in one patient. This erythrocyte enzyme deficiency is probably of no or minor significance for the biochemical and clinical pathogenesis of porphyria cutanea tarda. However, it may serve as a marker for genetic or type II porphyria cutanea tarda, which is characterized by an approximate 50% reduction of uroporphyrinogen decarboxylase activity in all tissues including erythrocytes and liver. In sporadic or type I porphyria cutanea tarda the enzyme defect is restricted to the liver (17). Although the classification of porphyria cutanea tarda may be more complex (17, 18), it can be assumed that uroporphyrinogen decarboxylase affection in most of our patients results from genetic factors, only for patient 7 (82% uroporphyrinogen decarboxylase activity in red blood cells) might the possibility of a type I porphyria cutanea tarda be considered. But even in this case genetic factors cannot be completely ruled out, as his brother (patient 6) and sister also suffered from porphyria cutanea tarda. The affection of hepatic uroporphyrinogen decarboxylase is thought to be the deciding factor for initiation of the disease process; liver uro-

Tab. 4 Enzyme activity in red blood cells.

	Activity of uroporphyrinogen decarboxylase [in % of healthy controls]	
Dual porphyria n = 7	50*	(33–83)**
Porphyria cutanea tarda n = 10	62	(50–76)

* = mean ** = range

porphyrinogen decarboxylase is also susceptible to toxic influences (1). As possible triggering factors for porphyria cutanea tarda, liver affection was found in three patients (2, 3 and 5); two of them (3 and 5) had been applying oral contraceptives.

Urinary coproporphyrin isomers I and III were analysed in three patients. An increased proportion of isomer I could be detected in two cases (2 and 5) as typical for cholestatic liver disease (4, 8), while patient 7 revealed a high level of urinary coproporphyrin III. This is characteristically found in acute hepatic porphyrias (4, 8); more sensitive than in urine, where coproporphyrin III is even under normal conditions the dominating isomer (normal 69–83% coproporphyrin III, 17–31% coproporphyrin I), an increase of isomer III can be proved in feces. In this specimen, healthy individuals excrete lower proportions of coproporphyrin III, ranging only between 25 and 40%, than in urine. An increase of the fecal coproporphyrin III proportion may be used as indicator for an acute hepatic porphyria, even when in a latent phase (4, 19). The determination of fecal coproporphyrin III could be performed in two of our patients (2 and 7); both of them revealed an elevated coproporphyrin III proportion (57%; 78%).

With the exception of higher urinary coproporphyrin values in our group, the porphyrin metabolite pattern of the seven patients presented here resembles the one which *Day* and coworkers (12) found in 25 South Africans and recognized as coexistent porphyria variegata and cutanea tarda. Some years later, *Sturrock* and coworkers reinvestigated 10 of *Day*'s patients and demonstrated the postulated enzyme defects of protoporphyrinogen oxidase (decreased by 45% in lymphocytes) and of uroporphyrinogen decarboxylase (decreased by 27% in lymphocytes and erythrocytes) (20).

Both genetic porphyria cutanea tarda and porphyria variegata follow an autosomal dominant trait of inheritance, though with a low clinical penetrance. The genes encoding uroporphyrinogen decarboxylase and protoporphyrinogen oxidase seem to be localized on different chromosomes: chromosome 1 for uroporphyrinogen decarboxylase and chromosome 14 for protoporphyrinogen oxidase (21). Although family investigations were not possible in this study, we suppose that our cases of dual porphyria result from the incidential genetic transmission of two independently occurring gene defects, most likely one from each parent. Therefore, with each parent being heterozygote for either porphyria cutanea tarda or porphyria variegata, their children had a 25% chance each of:

- becoming double heterozygotes for porphyria cutanea tarda and porphyria variegata,
- becoming heterozygote for porphyria cutanea tarda,
- becoming heterozygote for porphyria variegata,
- becoming not genetically predisposed.

An indication for this hypothesis could be seen in the sister of brothers 6 and 7, who suffered from porphyria cutanea tarda with no indication of variegata.

Another point of interest would be the question whether there was a special effect of this dual enzyme deficiency on the expression of porphyria cutanea tarda or variegata. Porphyria cutanea tarda is an accumulation disease of higher carboxylated porphyrins, mostly uro- and heptacarboxyporphyrin, which cause the typical photodermatosis when deposited in the skin. In contrast, porphyria variegata is a regulatory disorder of porphyrin metabolism caused by the excessive, uncontrolled induction of 5-aminolaevulinate synthase, the first and rate-limiting enzyme of heme biosynthesis, with the consequence of an increased supply of substrates for the enzymes along the heme synthetic pathway (16). This surplus of substrate might overtax a genetically afflicted uroporphyrinogen decarboxylase, thus increasing the dermal porphyrin deposition, which can be found in about one third of porphyria variegata cases, by additional amounts of (mainly) uro- and heptacarboxyporphyrin. It can be assumed that patients with a dual porphyria of cutanea tarda and variegata might at least be more susceptible for the development of photodermatosis. More investigations will be necessary to elucidate this question.

While in porphyria cutanea tarda the mobilization and successive renal elimination of accumulated liver porphyrins by low-dose chloroquine treatment has become a successful therapy (7, 22), in the case of dual variegate – cutanea tarda it should be considered that chloroquine sometimes induces acute porphyria manifestations (23). Therefore, chloroquine should either be omitted in these cases or, if the variegate is in a latent and stable phase (constantly normal urinary 5-aminolaevulinic acid and porphobilinogen levels), be applied under continuous clinical and pathobiochemical monitoring of urinary 5-aminolaevulinic acid, porphobilinogen and porphyrin excretion.

Acknowledgements

We thank Mrs. *S. Preis*, *S. Sauer* and *M. Wenz* for skilful technical assistance. This study was supported by the Hans-Fischer-Gesellschaft, Munich.

References

1. Kappas A, Sassa S, Galbraith RA, Nordmann Y. The porphyrias. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The metabolic basis of inherited disease. New York: McGraw-Hill, 1989:1305–65.
2. Doss MO. Porphyrien und Porphyrinstoffwechselstörungen. In: Classen M, Diehl V, Kochsiek K, editors. Innere Medizin. München: Urban & Schwarzenberg, 1991:802–13.
3. Doss M. Porphyrins and porphyrin precursors. In: Curtius HC, Roth M, editors. Clinical biochemistry. Principles and methods. Vol. II. New York: De Gruyter, 1974:1325–71.
4. Sieg I, Doss MO. HPLC der Koproporphyrin-I/III-Isomere bei hepatischen Porphyrinopathien. Lab Med 1992; 16:89–96.
5. Doss MO. Dual porphyria in double heterozygotes with porphobilinogen deaminase and uroporphyrinogen decarboxylase deficiencies. Clin Genet 1989; 35:146–51.
6. Herrero C, Vincente A, Bruguera M, Ercilla MG, Barrera JM, Vidal J, et al. Is hepatitis C virus infection a trigger of porphyria cutanea tarda? Lancet 1993; 1:788–9.
7. Köstler E, Doss MO. Die chronische hepatische Porphyrie (Porphyria cutanea tarda). In: Brandis M, Fanconi A, Frick P, Kochsiek K, Riecken EO, editors. Ergebnisse der Inneren Medizin und Kinderheilkunde. Heidelberg: Springer-Verlag, 1993:124–205.
8. Jacob K, Doss MO. Composition of urinary coproporphyrin isomers I–IV in human porphyrias. Eur J Clin Chem Clin Biochem 1993; 31:617–24.
9. McColl KEL, Thompson GG, Moore MR, Goldberg A, Church SE, Qadiri MR, et al. Chester porphyria: biochemical studies of a new form of acute porphyria. Lancet 1985; 2:796–9.
10. Doss M. New dual form of porphyria. Lancet 1988; 1:945–6.
11. Nordmann Y, Amram D, Deybach JC, Phung LN, Lesbros D. Coexistent hereditary coproporphyria and congenital erythropoietic porphyria (Günther disease). J Inher Metab Dis 1990; 13:687–91.
12. Day RS, Eales L, Meissner D. Coexistent variegate porphyria and porphyria cutanea tarda. N Engl J Med 1982; 307:36–41.
13. Meyer UA. Porphyrias. In: Braunwald E, Isselbacher KJ, Petersdorf RG, Wilson JD, Martin JB, Fauci AS, editors. Harrison's principles of internal medicine. New York: McGraw-Hill, 1987:1638–43.
14. Vaidya H. Dual porphyria – an underdiagnosed entity? Clin Chem 1987; 33:1190–3.
15. Doss M. Porphyrie. In: Thomas L, editor. Labor und Diagnose. Marburg: Medizinische Verlagsgesellschaft, 1992:547–77.
16. Doss MO. Hepatic porphyrias: pathobiochemical, diagnostic, and therapeutic implications. In: Popper H, Schaffner F, editors. Progress in liver diseases. New York: Grune & Stratton, 1982:573–97.
17. Elder GH, Roberts AG, de Salamanca RE. Genetics and pathogenesis of human uroporphyrinogen decarboxylase defects. Clin Biochem 1989; 22:163–8.
18. Hindmarsh JT. Enzyme heterogeneity in the porphyrias. Clin Biochem 1990; 23:371–4.
19. Doss M, Schermuly E. Urinary porphyrin excretion pattern and isomer distribution of I and III in human porphyrin disorders. In: Doss M, editor. Porphyrins in human diseases. Basel: Karger, 1976:189–204.
20. Sturrock ED, Meissner PN, Maeder DL, Kirsch RE. Uroporphyrinogen decarboxylase and protoporphyrinogen oxidase in dual porphyria. S Afr Med J 1989; 76:405–8.
21. Elder GH. Molecular genetics of disorders of haem biosynthesis. J Clin Pathol 1993; 46:977–81.
22. Ashton RE, Hawk JLM, Magnus IA. Low-dose oral chloroquine in the treatment of porphyria cutanea tarda. Brit J Dermatol 1984; 3:609–13.
23. Moore MR, McColl KEL. Therapy of the acute porphyrias. Clin Biochem 1989; 22:181–8.

Prof. Dr. med. M. O. Doss
Abteilung für Klinische Biochemie
Philipps-Universität
Deutschhausstraße 17½
D-35037 Marburg/Lahn
Germany